Pharmacological lipid lowering for prevention of cardiovascular disease in older adults



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Practice Points

- Dyslipidemia is a risk factor for cardiovascular disease (CVD) in older adults.
- Statin treatment should always be considered in secondary prevention.
- Data on primary prevention in older adults are scarce, but suggest that statin treatment should be considered for high-risk patients.
- As for all pharmacological treatment of older adults, treatment with statins should be individualized and factors such as life expectancy, quality of life, patient preferences, comorbidities and interaction with other drugs should be considered.
- Older adults are at increased risk of muscle-related adverse effects because of factors such as reduced renal or liver function, treatment with several interacting drugs, low body weight and altered metabolism. The dose of statin should be adapted and titrated slowly.
- Statin treatment is associated with an increased risk of Type 2 diabetes in older adults, but this risk is outweighed by the reduced risk of CVD. Glucose should be monitored in patients with other risk factors for diabetes. Healthy lifestyle habits should be encouraged.
- Measures to prevent CVD should be considered in older adults. If the special circumstances when treating older adults are considered, increased statin treatment has the potential to reduce or delay cardiovascular morbidity and mortality.

SUMMARY An increasing number of patients with cardiovascular disease (CVD) are older adults. New treatments have improved survival but also increased demand for prevention. Comorbidities in older adults contribute to low cholesterol, but accumulating data show that

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dyslipidemia is a risk factor for CVD in older adults. Although numerous studies show that statin treatment reduces CVD mortality and morbidity, few studies have targeted older adults specifically. However, *post-hoc* analyses of subgroups indicate that older adults may benefit from statin treatment. Risk reduction in secondary prevention is similar across all age groups, and the limited data available in primary prevention suggest that statins may be considered in high-risk older adult patients. However, statin therapy in older adults should be individualized, taking into account factors more common in this group.

In recent decades, there has been a dramatic reduction in the age-adjusted mortality from cardiovascular disease (CVD), most evident in ischemic heart disease (IHD), in western countries. However, CVD is still the major cause of death and the rates are increasing in developing countries [1]. Among older adults, CVD is still common, and indeed, an increasing fraction of the patients in coronary care units are old or very old [2]. In Sweden, the proportion of patients discharged from coronary care aged 85 years and over increased threefold for men and twofold for women between 1987 and 2009 (Figure 1). Coronary care has also improved among older adults with improving prognosis after the first myocardial infarction in patients over 80 years of age [3].

The changing cardiovascular epidemiology in older adults not only demands better coronary care but has also raised the issue of CVD prevention in this group [4-7]. Overall, hypercholesterolemia is the most established risk factor for CVD, and meta-analyses of randomized placebo-controlled studies have shown that intervention with statins to reduce low-density lipoprotein cholesterol (LDL-C) reduces CVD morbidity and mortality [8,9]. However, most data are derived from patients under 70 years of age and extrapolation to older adults has been questioned. Here we will review the current knowledge on pharmacological CVD prevention directed against dyslipidemia in older adults. Although focusing on pharmacological treatment, the importance of lifestyle should also be emphasized, including a proper diet, exercise and no tobacco smoking. The definition of elderly or older adult varies in different studies and in different meta-analyses. Some studies are referring to patients over 65 years of age while others have limit of 70 or even 80. In clinical practice the definition often has to be individual and based on the current status and the function of the patient.

Plasma lipid levels as risk factors in older adults

Serum total cholesterol (TC) and LDL-C are well-studied risk factors for CVD, and primarily IHD. However, TC and LDL-C have been questioned as risk factors in older adults [10,11], and several studies have reported that the association between cholesterol and risk of IHD is reduced with increasing age. The Framingham study reported a positive association between TC and IHD up to 70 years of age but not in individuals over 70 years; there is even an opposite trend in the relationship between TC and all-cause mortality in individuals over 80 years of age [12].

The negative association between cholesterol and mortality in older adults has been confirmed in several studies [13-17]. It is well known that cholesterol levels decrease in older adults, and low cholesterol is associated with several age-related conditions such as malnutrition and heart failure [14]. Furthermore, several studies have shown an association between low cholesterol and cancer [16,18-20]. In the Copenhagen heart study an overall association between low cholesterol and cancer was confirmed, but genetically decreased LDL-C was not associated with increased cancer [21]. This finding suggests that low TC does not primarily cause malignancies, and the association between low TC and death may be considered as a secondary phenomenon to non-CVD-related causes of death [14,21].

The weaker correlation between LDL-C and IHD in older adults may also result from survival selection. Subjects with high cholesterol are at higher risk of IHD when younger, but subjects who survive with high cholesterol may have other protective characteristics.

A recent meta-analysis on plasma lipid risk factors indicates that high TC is a significant risk factor for IHD mortality at all ages but is



Figure 1. Percentage of male and female patients aged ≥85 years among patients diagnosed with acute myocardial infarction in the Swedish National Hospital Discharge Registry 1987–2009. Reproduced with permission from [2].

highly attenuated in older adults (Figure 2), with a hazard ratio for lower IHD mortality associated with 1 mmol (38.7 mg/dl) cholesterol reduction of 0.45 for the youngest age group (40-49 years of age) and 0.85 for the oldest (80-89 years of age) [22]. However, although the relative risk reduction is reduced in the oldest subjects, the increased frequency of IHD means that the absolute number of cases associated with cholesterol is highest in this group [22]. This metaanalysis also shows that IHD mortality is negatively associated with high-density lipoprotein cholesterol (HDL-C) and positively associated with non-HDL-C and TC/HDL-C at all age groups. However, the association with HDL-C also reduces with age [22].

In recent studies lipoprotein(a) (Lp(a)) has been confirmed as an important additional risk factor [23,24]. Data from mendelian randomization studies also suggest that high Lp(a) is a cause of CVD [23]. Lp(a) was shown to be a strong risk factor for CVD in men but not women in a prospective study of a large cohort aged over 65 years and initially without CVD [25].

An association between lipids and lipoproteins and stroke is absent in older adults [22,26]. A recent meta-analysis showed a weak correlation between TC and stroke in the young but not in subjects aged over 60 [22].

Prevention of CVD in older adults by reducing risk factors when young

The most important way to prevent CVD in older adults is to promote a healthy lifestyle and reduction of risk factors early in life. In a Gothenburg (Sweden) study of men born in 1913, men who reached the age of 90 years were nonsmokers, had low cholesterol and higher socioeconomic status at 50 years [27]. Similarly, follow-up of the Gothenburg primary prevention study showed that conventional risk factor burden in middleage was highly prognostic for IHD and all-cause mortality over the following 35 years [26].

Similar results have been shown for lifetime risk. In a recent analysis of data from 18 cohort studies involving 257,384 black and white men, participants with an optimal risk factor profile when aged 55 had a much lower risk of CVD-related death before the age of 80 than those with two or more risk factors (4.7 vs 29.6% among men and 6.4 vs 20.5% among women) [28]. Similar data on lifetime risk based on risk factor patterns at age 50 have been shown in a report from the Framingham heart study [29].



Figure 2. Age-specific associations between ischemic heart disease mortality and usual total cholesterol. Hazard ratios are plotted on a floating absolute scale of risk (so each log hazard ratio has an appropriate variance assigned to it). Each square has an area inversely proportional to the variance of the log of the hazard ratio that it represents.

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Prevention of CVD with statins in older adults

Secondary prevention of CVD

Data derived from controlled studies targeting older subjects are limited, but this group was specifically studied in the PROSPER and the SAGE trials. PROSPER included patients aged 70–82 years with CVD or at high risk for CVD [30]. Patients were treated with pravastatin 40 mg daily or placebo. A 15% IHD reduction was found, whereas no reduction in stroke was observed. Subgroup analyses showed that the significant reduction was limited to secondary prevention and no significant effect was seen in patients free from CVD at inclusion. Thus, PROSPER supports the use of statins in secondary prevention up to the age of approximately 80 years. In the SAGE trial, 893 patients aged 65–85 years with stable IHD were recruited and randomized to atorvastatin 80 mg or pravastatin 40 mg daily [31]. Atorvastatin treatment resulted in lower LDL-C, reduced all-cause mortality (hazard ratio: 0.33) and a nonsignificant trend towards reduced major IHD events [31].

Post hoc subgroup analyses of older adult subjects from secondary prevention randomized statin studies are summarized in Table 1. In general, the relative risk reduction in patients aged up to at least 75–80 years is similar to that in younger patients. The higher cardiovascular morbidity in older adults often makes the absolute effect of statins up to two times higher.

The Scandinavian Simvastatin Survival Study (4S), which was the first statin trial, included 4444 IHD patients aged >65 years who were treated for approximately 5 years with simvastatin 20–40 mg daily or placebo [32]. A subgroup analysis of patients over 65 years (827 women and 1021 men) demonstrated that the risk reduction in this older adult group was similar to that obtained in the whole study [33]. In men, all-cause mortality was reduced by 34%, IHD mortality by 43% and major coronary events by 34%. Similar reductions in relative risk were obtained in women, but there were too few deaths to assess effects on mortality in women.

Another major study is the Heart Protection Study in which 20,536 high-risk individuals aged 65–70 years were allocated to simvastatin 40 mg daily or placebo [34]. After 5 year's treatment, there was an 18% reduction in coronary death and an approximate 25% reduction in coronary events. A subgroup analysis demonstrated that these reductions were similar in all age groups (9839 individuals <65 years of age; 4891 individuals >65 and <70 years of age; and 5806 of >70 years of age). This study also reported a 25% reduction in stroke following statin treatment.

Similar results were shown by subgroup analysis of the secondary preventive LIPID trial, which included 3514 patients aged 65–75 years treated with pravastatin 40 mg daily or placebo [35]. All-cause mortality, CVD mortality and CVD events were reduced by more than 20% in patients over 65 years of age. From these data, the authors calculated that per 1000 persons treated, 45 deaths and 47 major coronary events would be prevented in the older group over 6 years compared with 22 deaths and 32 major coronary events in the younger patients over the same time period.

Subgroup analysis of the CARE trial was performed on 1283 patients aged 65–75 years (mean age of 69 years) who had experienced a myocardial infarction and were treated with pravastatin 40 mg daily or placebo for 5 years [36]. Statin treatment resulted in a relative reduction of 35% for IHD events, 40% for coronary death and 40% for stroke. The numbers needed to treat for 5 years to prevent one major coronary event and one coronary death in older patients was 11 and 22, respectively.

In the TNT trial, in which 3809 patients aged over 65 years with coronary disease were randomized to 80 or 10 mg atorvastatin daily, the higher dose resulted in a relative risk reduction of 19% for major cardiovascular events [37]. Differences between the doses for other end points had nonsignificant trends.

In some of the published meta-analyses, subgroups according to age are reported. In a metaanalysis performed by the Cholesterol Treatment Trialists' Collaboration, rate ratios for the effect of statins on major vascular events were 0.78, 0.78, 0.84 in age groups <65, 65–75 and >75, respectively [8]. Thus, the risk reduction from statin treatment was equal in all age groups. A meta-analysis of patients with diabetes treated with statins demonstrated similar risk reductions in patients aged above and below 65 years [38].

Since data on patients above 80 years are scarce, an observational study from the Swedish Heart Intensive Care Register is of interest [39]. This study included all patients in the register aged over 80 years at admission for a myocardial infarction during 1999-2003 (21,000 patients in total). All-cause mortality was significantly lower in patients receiving statins at discharge (relative risk: 0.55). To reduce bias due to comorbidity, additional analyses excluded patients who died within 14 days or 365 days of discharge. In these analyses, relative risks for all-cause mortality were 0.62 and 0.64, respectively. No increase in cancer with statin treatment was observed. Although observational, this study supports statin treatment in secondary CVD prevention of the very old.

Primary prevention of CVD

Data from statin studies on primary prevention in older adult groups are very limited, but some studies have performed subgroup analysis to

Table 1. <i>Post-hoc</i> subgroup analyses of older adults subjects from randomized studies on statin treatment.						
Study	Authors (year)	Treatment	Prevention level and age subgroup	Results	Ref.	
4S	Miettinen <i>et al.</i> (1997)	Simvastatin 20–40 mg vs placebo	Secondary prevention. Subgroup >65 years	CVD end points reduced by 30-40%	[33]	
CARE	Lewis <i>et al.</i> (1998)	Pravastatin 40 mg vs placebo	Secondary prevention. Subgroup 65–75 years	CVD end points reduced by 30-40%	[36]	
LIPID	Hunt <i>et al</i> . (2001)	Pravastatin 40 mg vs placebo	Secondary prevention. Subgroup 65–75 years	CVD end points reduced by >20%	[35]	
HPS	HPS Collaborative Group (2002)	Simvastatin 40 mg vs placebo	Primary plus secondary, high-risk patients. Subgroup 65–70 years	CVD end points and total mortality reduced by >30%. Stroke reduced by 25%	[34]	
PROSPER	Shepherd <i>et al.</i> (2002)	Pravastatin 40 mg vs placebo	Primary and secondary prevention. Age 70–82 years	Mixed end points reduced by 15%. Only significant in secondary prevention	[30]	
TNT	Wenger <i>et al.</i> (2007)	Atorvastatin 80 vs 10 mg	Secondary prevention. Subgroup >65 years	Relative risk reduction for IHD events 19% in favor of the high dose	[37]	
SAGE	Deedwania <i>et al.</i> (2007)	Atorvastatin 80 mg vs pravastatin 40 mg	Secondary prevention. Subgroup 65–85 years old with IHD	Atorvastatin reduced total mortality by 67% and major IHD events by 29%	[31]	
AFSCAP/ TexCAPS	Downs <i>et al.</i> (1998)	Lovastatin 20–40 mg vs placebo	Primary prevention in high-risk patients. Subgroup > median age (57 for men, 62 for women)	Relative risk reduction of 40% for composite CVD end point	[40]	
JUPITER	Glynn <i>et al</i> . (2010)	Rosuvastatin 40 mg vs placebo	Primary prevention. Subgroup >70 years	Combined IHD end point reduced by 39%	[41]	
CVD: Coronary h	eart disease: IHD: Ischemi	ic heart disease.				

assess if benefit from statin treatment is also significant in older adults. The AFSCAP/TEXCAP study included 6605 patients up to 73 years of age [40]. Subjects did not have CVD at baseline and were treated with lovastatin or placebo. The relative risk reduction was similar in subjects above and below the median age (57 years for men; 62 years for women). The risk reduction was approximately 40% for composite CVD end points in both groups.

The JUPITER trial was designed to test the effect of rosuvastatin versus placebo and included 18,000 subjects without CVD and with LDL-C below 3.7 mmol/l (147.1 mg/dl) and CRP above 2.0 mg/l [41]. The study was stopped prematurely due to the effect of treatment (a 30% reduction in IHD). A *post hoc* analysis divided subjects according to their age (below and above 70 years); 32% of participants were 70 years or older [41]. The relative reduction for a composite CVD primary end point was similar in subjects below and above 70. The number of participants needed to be treated for 4 years to prevent one major event was 24 in the older group and 36 in the younger age group.

Other lipid-lowering drugs

Data on other lipid-lowering drugs in CVD prevention are, in general, less convincing. In a number of studies, fibrates have been found to reduce CVD morbidity, shown most convincingly in *post hoc* analyses of patients with low HDL and high triglycerides [42,43]. A recent meta-analysis showed that fibrate treatment reduces CVD events by 13%, the benefits being most robust in patients with high triglyceride levels (>2.3 mmol/l; 203.7 mg/dl) and with similar risk reduction in patients above (up to 79) and below 60 years of age [44].

Studies specifically directed toward older adults are missing and conclusions have to be extrapolated from available studies. Some guidelines recommend fibrates to high-risk patients with hypertriglyceridemia (>2.3 mmol/l; 203.7 mg/dl) that persists after lifestyle adjustment or statin treatment [45]. A similar approach may also be considered in selected cases for older adult patients. Patients with severe hypertriglyceridemia (triglycerides >10 mmol/l; 885.7 mg/dl) should be treated with a fibrate to prevent pancreatitis.

Cholesterol absorption inhibitors such as ezetimibe are primarily used in combination with statins when lipid targets are not reached or in cases of statin intolerance. Ezetimibe reduces LDL-C by 15–20% on top of the reduction obtained with a statin. Data on clinical end points are missing in general and therefore also in older adults. Bile-acid-binding drugs also reduce LDL-C by approximately 20%. According to current guidelines, bile-acid-binding drugs and ezetimibe may be considered in patients where targets are not reached or in patients with statin intolerance.

Niacin is effective in reduction of triglyceride and LDL-C levels and has in one clinical trial been shown to reduce CVD [46]. The use of niacin is limited by its side effects and data specifically targeting older adults are missing. Furthermore, after two recent negative trials [47,48] niacin is no longer available on the European market and its use in cardiovascular prevention is being re-evaluated.

Treatment targets

In some guidelines, suggested treatment targets are based on current knowledge from trials and meta-analyses [45,49]. In the recent European guidelines, the targets differ in the different CVD risk groups [50]. The LDL-C targets for patients with very high risk, high risk and moderate risk are 1.8, 2.5 and 3.0 mmol/l (70, 100 and 115 mg/dl), respectively. Risk estimation algorithms are often not applicable to older adults. The upper limit for SCORE and PROCAM algorithms are 65 years [51,52], while for the Framingham risk score the upper limit is 74 years [53]. In older adults risk estimation has to therefore be individualized from clinical judgment. Although several studies suggest that benefit from statin treatment is similar in older and younger patients, the same treatment targets cannot be extrapolated to older adults. Several factors have to be considered that will affect possibilities to treat, indications to treat and targets for treatment.

Conditions to be considered in older adults

Treatment of older adult patients has to be individualized to a greater extent than for middle-aged patients. Before starting treatment, factors such as comorbidities, life expectancy, quality of life and patient preferences should be carefully considered and discussed with the patient. Individualized treatment, good clinical judgment and communication with the patient are most important and cannot be substituted by guidelines.

As for all pharmacological treatment of older adults, factors to be considered include polypharmacy, reduced liver or kidney function, the overall balance in lean and fat mass as well as muscular performance and intestinal absorption [4]. A large number of drugs that are frequently used in older adults may interact with statins [54]. Therefore, the statin dose often has to be lower and titrated over a longer time period compared with younger patients.

Adverse effects of statins

The most important adverse effects during statin treatment are muscle symptoms [55,56]. These can vary from myalgia, without elevation of creatine kinase (CK), to severe myopathy (rhabdomyolysis) with muscular necrosis, myoglobinuria and renal failure. Pain and tenderness typically affect the larger proximal muscle groups, but there are several reports of muscle symptoms in more atypical locations. The diagnosis can be difficult to establish since symptoms are often vague and pain from other causes such as rheumatologic conditions, hypothyroidism, frailty and possibly severe vitamin D deficiency, have to be excluded. CK levels should be checked, but they are normal in many cases of myalgia. If CK levels are normal, statin therapy may continue if symptoms are acceptable to the patient. If CK is moderately elevated (<5× the upper limit of normal), CK should be checked and statin treatment should be reconsidered if CK remains elevated. If CK is higher, more severe myopathy should be suspected, the statin should be stopped and CK rechecked. In rhabdomyolysis, CK is elevated to $>10\times$ the upper limit of normal.

The frequency of myalgia varies from 1.5-5%in randomized studies [57,58] to 5-10% in observational studies. The incidence of rhabdomyolysis is estimated to be 1-3 cases per 100,000 patient years [58].

In older adults, even mild muscle symptoms may cause incapacity and have a major impact on quality of life. Older adults are a risk group for myopathy and have many of the characteristics predisposing to statin-induced myopathy (e.g., low body weight, reduced renal or liver function, changed lean body mass vs body fat, change in plasma albumin concentration and interaction with other drugs) [59]. In the JUPITER trial, muscle symptoms were more frequent in older adults than in younger subjects, but the difference was not significant [41]. This may explain some of the lower adherence to statin treatment that was observed in the IDEAL trial [60].

Mild-to-moderate elevations of hepatic transaminase levels are commonly observed in patients taking statins, but are infrequently attributable to statin therapy. The elevation is, in general, not associated with clinical symptoms or liver function abnormalities. The effect is dose related and low-to-moderate doses of statins are seldom associated with significant elevation of transaminases [61,62]. Maximal doses of the more potent statins are associated with elevation of transaminases.

Until recently, routine control of transaminases was recommended during statin treatment. This recommendation has recently been changed. In 2006, the National Lipid Association published an assessment on statin safety and reported that clinically significant liver disease was extremely uncommon during statin treatment [63,64]. In 2012, the US FDA changed their recommendation to state that transaminases should be checked before the start of treatment, but only during treatment if there are clinical indications [59]. In the randomized statin studies listed in Table 1, transaminase elevation did not seem to be more frequent in older adults than in middle-aged patients. However, it should be noted that the patients in the trials are selected to exclude comorbidities, reduced renal and liver function, and interfering medication. The possibility of adverse events affecting the liver should therefore be considered when statins are administered to more susceptible patients.

A large number of drugs may interfere with the metabolism of statins and the possibility of interactions should be considered, especially in older adults (Table 2). Many drugs are metabolized by the CYP3A4 enzyme, and thus the

Table 2. Drugs potentially interacting with statins leading to increased risk of myopathy and rhabdomyolysis.

Anti-infective agents	Calcium antagonists	Other
ltraconazole	Verapamil	Cyclosporine
Ketoconazole	Diltiazem	Danazol
Posaconazole	Amlodipine	Amiodarone
Erythromycin	_	Ranolazine
Clarithromycin	-	Grapefruit juice
Telithromycin	-	Nefazodone
HIV protease inhibitors	-	Gemfibrozil
Data taken from [72,73].		

CYP3A4-dependent statins (simvastatin, lovastatin and atorvastatin) may be more susceptible to interactions [58].

A higher onset frequency of Type 2 diabetes in patients treated with statins has recently been shown and verified in several meta-analyses of controlled statin trials [65-68]. The frequency is generally low (9% increased risk) and is far outweighed by the protective effect of statins. The data transfers to one extra case of Type 2 diabetes for 255 patients treated with statin for 4 years. Over the same period 5.4 CVD events per mmol/l of LDL-C would have been prevented. However, patients with risk factors for diabetes, such as increased weight or insulin resistance, and older adults are at increased risk of developing diabetes when treated with statins. The increased risk is dose dependent and higher with high doses of the potent statins. In older adults, especially in primary prevention, or in the presence of risk factors for diabetes, monitoring of glucose should be considered.

Development of dementia during statin treatment has been discussed [69]. However, in recent meta-analyses no support for increased risk for dementia has been found, rather there is a tendency towards reduced development of dementia during statin treatment [70.71].

Conclusion & future perspective

Dyslipidemia is a risk factor for CVD at all ages but is attenuated in older adults. Cholesterol levels in older adults are often modified by comorbidities causing low cholesterol and increased mortality.

The best approach to prevent CVD in old age is to intervene to improve risk factors early in life, through lifestyle modifications and pharmacological intervention. Risk factor burden in middleage is a strong predictor of CVD in older adults.

Many studies, mostly *post-hoc* analyses, support intervention to lower LDL-C with

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statins in secondary prevention in older adults. The available data for primary prevention are limited but suggest that statin therapy may be considered for patients at high risk of developing CVD.

Statin therapy in older adults should be individualized, taking into account factors more common among older adults, such as low body weight, hepatic or renal dysfunction, other comorbidities, drug interactions, life expectancy and future quality of life. These factors increase the risk for adverse effects, primarily myalgia or myopathy. In older adults, the risk of statininduced diabetes is increased and glucose levels should be monitored. However, the risk of diabetes is far outweighed by the reduction in CVD during statin treatment.

With further reduction in morbidity and mortality among the young and middle-aged, we should expect an increasing number of CVD patients among older adults. Demands for treatment, but also for prevention will increase. Older adults patients are undertreated with statins, and increased statin treatment of older patients has the potential to reduce or delay CVD mortality.

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